

### Remarks

Prior to examination, applicants request entry of the present amendment and remarks.

Claims 4, 5, 8 and 11 are pending in this application. Claims 1-3, 6, 7, 9 and 10 are cancelled.

The Amendment to claims 4 and 5 makes it clear that 3mg/kg dosage of Desmyter (line 5 of the 6th paragraph on page 518) does not fall within the range of the present claims.

With regard to the Examiner's question of "chiefly in the liver", applicants submit new data suggesting that the complex of poly(I):poly(C) with the cationic liposome (LIC-101) according to the present invention can induce interferon (IFN) chiefly in the liver of cynomolgus monkeys. See the attached Tables 1 and 2.

Table 1 shows that the complex containing poly(I):poly(C) is localized chiefly in the liver after an intravenous infusion to a cynomolgus monkey.

Table 2 shows that IFN- $\beta$  is induced in the liver of cynomolgus monkeys three hours after the intravenous injection of the complex containing poly(I):poly(C). IFN- $\beta$  is detected in the liver, but not in the serum three hours after the administration of the complex. From Tables 1 and 2, it is apparent that the complex containing poly(I):poly(C) can be taken specifically into the liver and induce IFN- $\beta$  chiefly in the liver.

With regard to the correlation between the length of poly(I):poly(C) and production of INF, applicants refer to the attached Table 3.

Table 3 shows that the longer the average chain length of poly(I):poly(C) is, the more IFN-beta is induced. From Table 3, it is apparent that the chain length of poly(I):poly(C) correlates with production of interferon.

In the case of 500-600 bp poly(I):poly(C) alone instead of the complex containing poly(I):poly(C), even 100ng/ml thereof can hardly induce IFN.

**Table 1 . Localization of radioactivity (% of dose) in main tissues after an intravenous infusion of [<sup>3</sup>H]poly(I):poly(C)/LIC-101 to a cynomolgus monkey (n = 1)**

|  |        | Localization of radioactivity (% of dose) |      |      |
|--|--------|---|------|------|
|  |        | 0.083 h                                   | 1 h  | 4 h  |
| [ <sup>3</sup> H-, <sup>14</sup> C-]<br>poly(I):poly(C)/<br>LIC-101<br>( <sup>3</sup> H-Poly(C)) | Plasma | 50.5                                      | 4.9  | 1.9  |
|  | Heart  | 0.3                                       | 0.9  | 0.7  |
|  | Liver  | 78.2                                      | 45.1 | 10.7 |
|  | Lung   | 1.2                                       | 0.6  | 0.7  |
|  | Kidney | 1.8                                       | 4.5  | 5.4  |
|  | Spleen | 2.5                                       | 2.1  | 1.3  |

Dose: 0.1 mg/kg [<sup>3</sup>H]poly(I):poly(C)/LIC-101

LIC-101 is a cationic liposome consisting essentially of 2-O-(2-diethylaminoethyl) carbamoyl-1, 3-dioleoylglycerol and lecithin.

poly(I):poly(C)/LIC-101 means a complex of poly(I):poly(C) with LIC-101.

**Table 2. Induction of IFN-beta in Cynomolgus monkeys by [<sup>3</sup>H]poly(I):poly(C)/LIC-101**

Poly(I):poly(C)/LIC-101 was administered to Cynomolgus monkeys by intravenous injection. Three hours after the administration, the amount of IFN-beta in the liver and serum was measured by a human IFN-beta ELISA kit. The amount of IFN-beta was determined as IU/ml (Serum) or IU/g (Liver) in the table.

|                              | Serum            | Liver           |
|------------------------------|------------------|-----------------|
|                              | IFN-beta (IU/ml) | IFN-beta (IU/g) |
| Control                      | n.d.             | n.d.            |
| Monkey number 1, 0.025 mg/kg | n.d.             | 35.6            |
| Monkey number 2, 0.025 mg/kg | n.d.             | 41.7            |
| Monkey number 3, 0.1 mg/kg   | n.d.             | 50.1            |
| Monkey number 3, 0.1 mg/kg   | n.d.             | 86.0            |

n.d.: not determined

Table 3. Induction of IFN-beta in HeLaS3 cells by poly(I):poly(C)/LIC-101

HeLaS3 cells were seeded at a density of  $10^4$  cells/well (96-well plate). The various length of poly(I):poly(C) and LIC-101 complexes were added to cells. Incubation was continued for 24 h. The amount of IFN-beta in the cell culture medium was measured by a human IFN-beta ELISA kit. The amount of IFN-beta was determined as IU/ml in the table.

| Average chane length of<br>poly(I):poly(C) (bp) | Concentration of poly(I):poly(C)/LIC-101 |         |          |
|---|--|---------|----------|
|   | 1ng/ml                                   | 10ng/ml | 100ng/ml |
| 500- 600  | 0  | 36      | 190      |
| 300   | 0  | 34      | 130      |
| 150   | 0  | 20      | 92       |
| 80- 100   | 0  | 14      | 48       |
| 50- 60  | 0  | 12      | 36       |
| 20- 30  | 0  | 0       | 0        |

It is urged that the present amendment and remarks address the Examiner's remarks in the Advisory Action issued in the parent application. Reconsideration and withdrawal of the rejections pending in the parent is requested.

It is believed that all of the present claims are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited.

### AUTHORIZATION

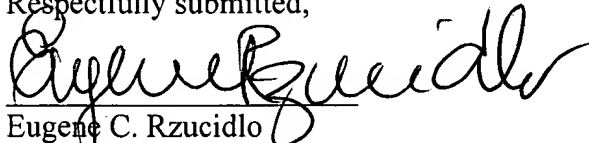
If the Examiner believes that issues may be resolved by telephone interview, the Examiner is respectfully urged to telephone the undersigned at (212) 801-2146. The undersigned may also be contacted by e-mail at [ecr@gtlaw.com](mailto:ecr@gtlaw.com).

No additional fee is believed to be necessary. The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 50-1561.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-1561.

Dated: July 28, 2005

By: Respectfully submitted,



Eugene C. Rzucidlo  
Registration No. 31,900  
Customer Number: 32361